Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2013 to 31st March 2014

DATE OF ISSUE: 19th February 2016

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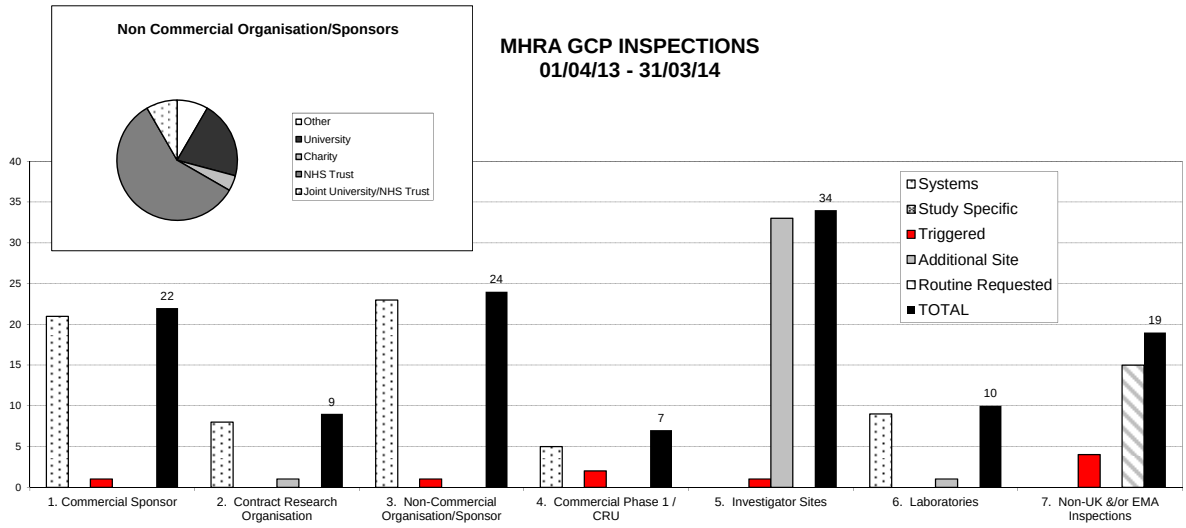
1. INTRODUCTION

This report covers the metrics period 1st April 2013 to 31st March 2014.

2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 125 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are presented below.

The number of inspections of non-commercial organisations was 24, of commercial sponsors was 22, of Contract Research Organisations (CROs) was 9, of investigator sites there were 34 and finally there were 7 phase 1 unit inspections. GCP inspections of UK laboratory facilities conducting clinical trial sample analysis is generally conducted by the MHRA Laboratories Inspectorate and there were 10 inspections, however, 1 of these was performed by the GCP inspectorate as an associated site. The number of non-UK and EMA inspections was 19. Triggered inspections were carried out as a result of information received by the GCP Inspectorate, for example in response to a serious breach report, and triggered inspections were undertaken of different organisations. For triggered inspections, 1 was a commercial sponsor, 1 was a joint inspection of 2 non-commercial co-sponsors, 2 were of phase 1 units, 1 was of an investigator site and 4 were non-UK/EMA inspections, the latter triggered by CHMP.

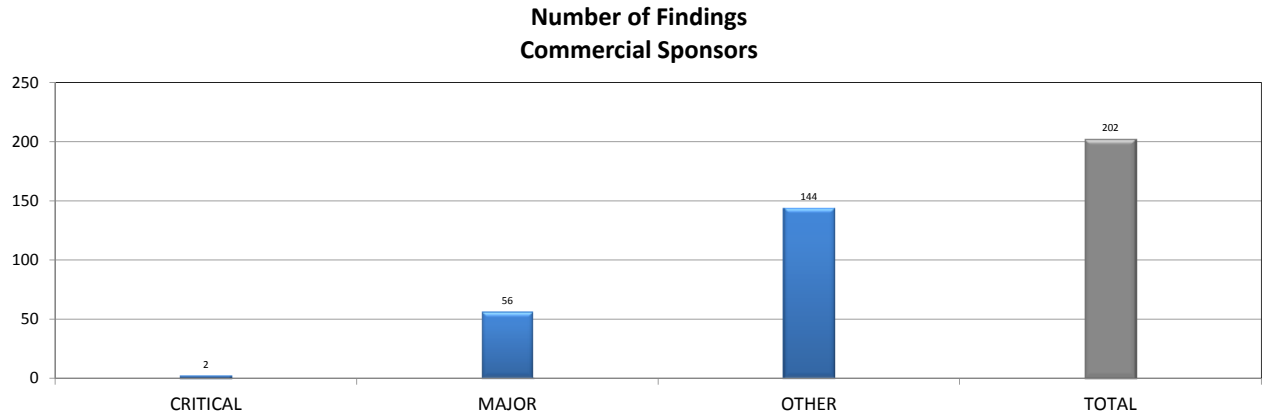


3. INSPECTION REPORTS AND FINDINGS

Reports relating only to the inspections carried out in the Metrics Period were reviewed. It is important to note that multiple inspections can be reported in one GCP Inspection Report, for example, a commercial sponsor GCP Inspection Report may consist of the sponsor inspection and associated investigator site inspections. Where an inspection was conducted before 1st April 2013 and the other associated inspections were conducted after 1st April 2013 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted after 1st April 2013 (e.g. investigator site(s)) will be included in this metrics report, as these were inspections conducted during this Metrics Period. The findings reported in this document cover UK site inspections only. Metrics from inspections requested by the European Medicines Agency (EMA) are produced by the EMA. The findings are those that were contained in the inspection reports and do not take into account any inspection responses, apart from in the explanatory text for critical findings. The metrics data entry had an independent sample Quality Control (QC) check.

3.1 Commercial Sponsors (Routine Systems, Study Specific and Triggered)

A total of 22 commercial sponsors were inspected and all have been reported. Of the 22 inspections, 2 (9.1%) had at least one critical finding and 19 (86.4%) had at least one major and/or critical finding. The total number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Commercial Sponsors)

	Mean	Median	Mode	Maximum	n
Critical	0.1	0.0	0.0	1	22
Major	2.5	3.0	3.0	6	22
Other	6.5	6.0	6.0	12	22

There were 2 critical findings from 2 organisations.

Critical Finding 1

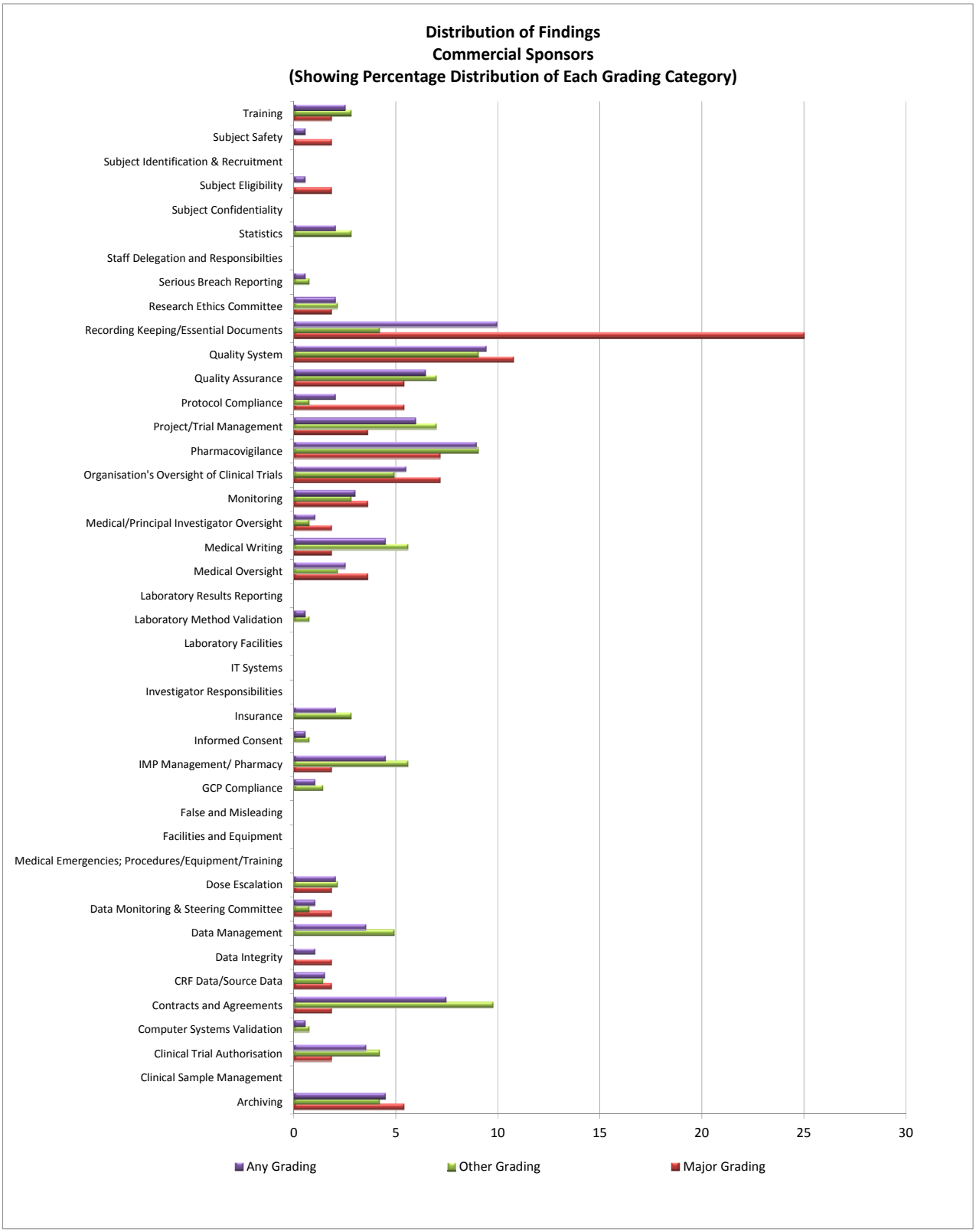
The critical finding was for Data Integrity and concerned a trial examined where the electronic diaries were used by the trial subjects to record details of IMP administration, any bleeding episodes, and responses to treatment. There were changes to subject-reported data that had been requested by investigator site staff and accepted in the study databases that were not supported by adequate source data; that is, there was no contemporaneous source record of the discussion between the investigator site staff and the subject or caregiver and the reason for the change. The issues were not limited to a specific site or country. Additionally, there was insufficient oversight by the sponsor of the vendor providing the electronic diaries and the diaries were being used despite key functionality not working, and the diary being confirmed as a validated computer system. This was a “critical” finding due to the number of records affected and the direct link between subject-reported data and key study endpoints in 4 trials.

Critical Finding 2

The critical finding was for Pharmacovigilance regarding failures to comply with regulatory reporting requirements. The first issue was the failure to report Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Research Ethics Committee (REC), with only 2/17 reported for one trial examined. This was confirmed as a systemic issue with data showing 37.7% of SUSARs had not been

reported to the REC in the required timeframe in a 4 year period prior to the inspection. Reporting to the MHRA was also late for some of these SUSAR cases, but at 5.2%, this was not as prevalent as for REC reporting. Additionally, there was evidence of failure to submit a Development Safety Update Report (DSUR) to the REC and implementing an updated Reference Safety Information (RSI) to assess adverse reactions without approval of this substantial change by the MHRA.

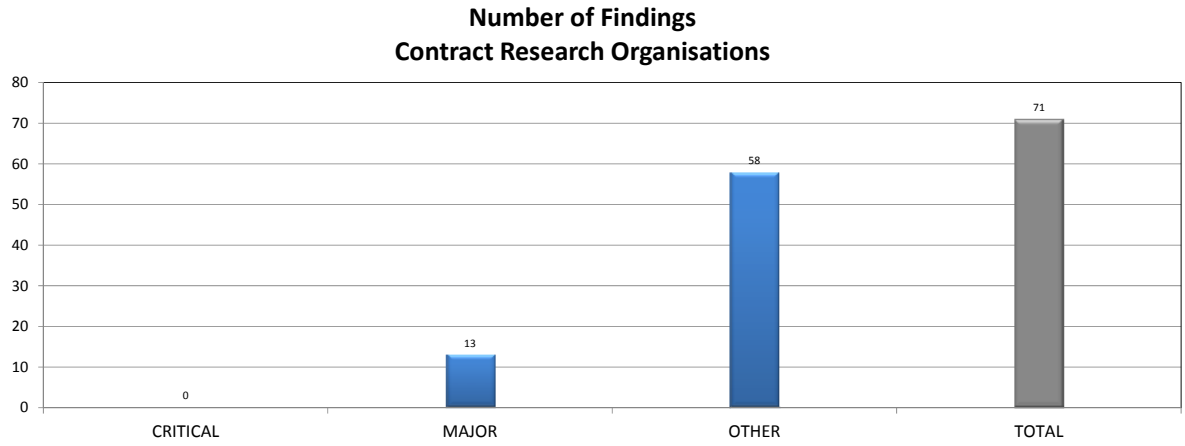
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Commercial Sponsors
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
25
30
Any Grading
Other Grading
Major Grading

3.2 Contract Research Organisations (CRO) (Routine Systems and Triggered)

A total of 9 Contract Research Organisations were inspected and all have been reported. One of these was as an additional site as a part of a commercial sponsor inspection.

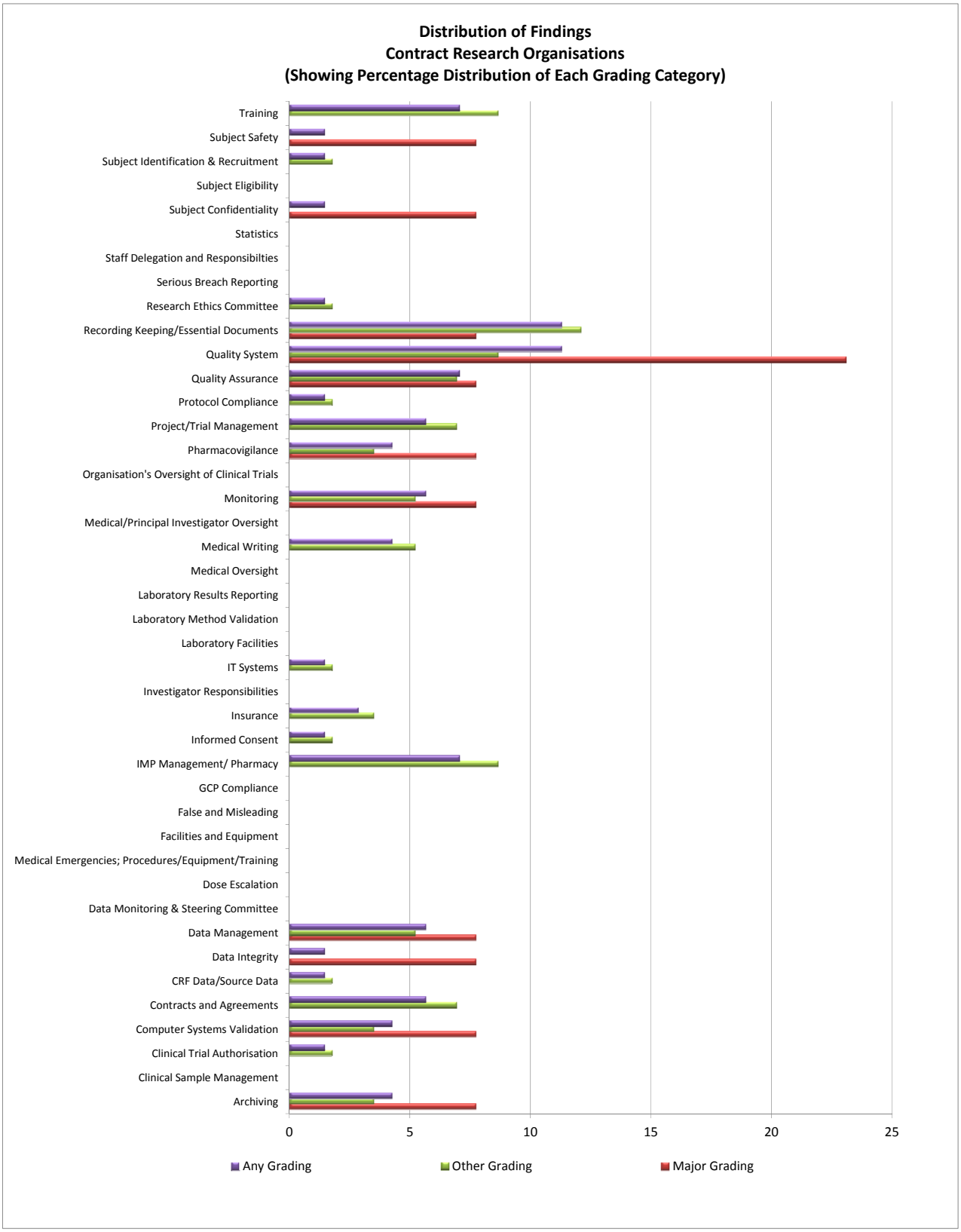
Of the 9 inspections, none had any critical findings and 7 (77.8%) had at least one major finding. The total number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Contract Research Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	9
Major	1.4	1.0	1.0	4	9
Other	6.4	5.0	5.0	12	9

The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Contract Research Organisations
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
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Laboratory Results Reporting
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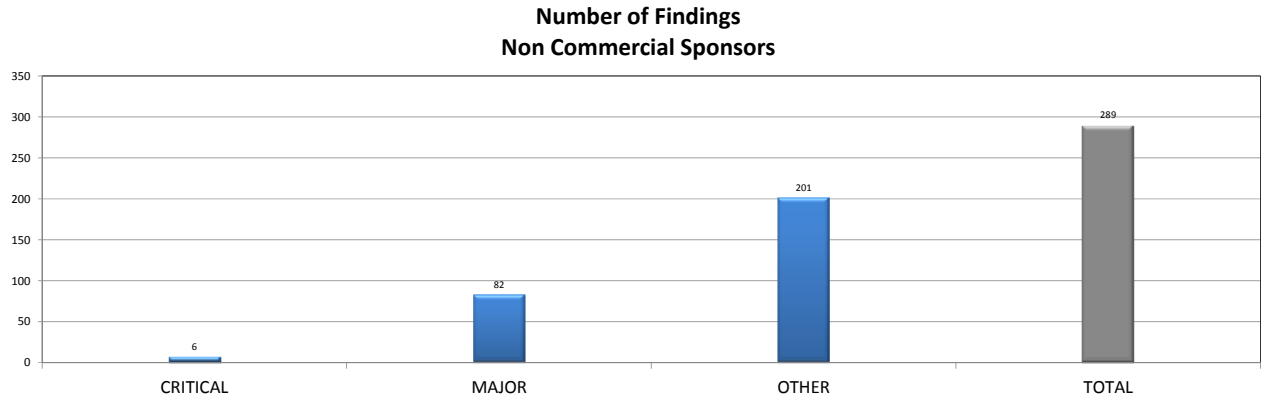
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
25
Any Grading
Other Grading
Major Grading

3.3 Non Commercial Organisations (Routine Systems and Triggered)

A total of 24 non-commercial organisations were inspected, 5 were of Universities, 14 were of NHS Trusts, 1 was a charitable organisation, 2 were joint inspections of a NHS Trust and University and 2 were other types of non-commercial organisation. Some of the non-commercial organisations were clinical trial units, which are inspected in their own right. All have been reported.

Of the 24 inspections, 5 (20.8%) had at least one critical finding and 23 (95.8%) had at least one major and/or critical finding. The number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Non Commercial Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.3	0.0	0.0	2	24
Major	3.4	3.0	3.0	9	24
Other	8.4	8.0	10.0	15	24

There were 3 (findings 1-3 below) critical findings identified from 3 different organisations, which were a charity, an NHS Trust and a University Clinical Trials Unit. A university had 1 critical finding (finding 4 below) from a routine systems inspection and this triggered a further inspection. This triggered inspection was of the university and a NHS Trust who were co-sponsors and a joint inspection report was issued that awarded the co-sponsors 2 critical findings (findings 5 and 6 below) from the same trigged inspection.

Critical Finding 1

One critical finding for the charitable organisation was for Data Integrity. The process for the conduct of a “best response evaluation” and the management of the subsequent data generated was not robust leading to incorrect efficacy data being reported and discussed in the trial report published in an academic journal. The finding was made up of a number of individual findings, which when taken together illustrated the lack of data integrity for this evaluation. The sponsor had decided to implement an additional assessment of response as requested by the Chief Investigator – ‘very good partial response’, based on a recent publication, which added an additional category and was to be derived from existing data by the data managers. The process for determining this additional category was relatively complicated and relied on a complete data set; a good understanding of the disease and an

understanding of the data previously collected. From review on inspection, the process appeared perfunctory; utilised an incomplete data set with ~40% of the data being incomplete requiring data queries to be answered by the clinical sites; utilised a temporary member of staff with a limited understanding of the disease and associated data; the re-evaluation process was not defined in appropriate procedures; and finally not subject to effective quality control checks. Ultimately this data was reported in a prominent journal and found to contain a number of basic errors regarding the number of patients per category, and there was no evidence that the data queries were ever submitted or resolved suggesting that this table was based on an incomplete and inaccurate data set.

Critical Finding 2

A critical finding for Archiving was reported for an NHS Trust. The Trust as sponsor had failed to implement an archiving system that ensured compliance with the clinical trial archiving regulations. There was no named Archivist for the Trust. Responsibility for archiving was delegated to investigators, but there was no procedure in place for investigators to follow defining how archiving should be done, nor what the retention period should be. This procedural aspect was also highlighted at the previous MHRA GCP inspection, but the Trust had failed to implement CAPA in relation to this finding. The Trust had archived clinical trial documentation, including source documentation, in an off-site archiving facility. This facility was then flooded, but no serious breach was reported related to this. As archiving had been delegated to investigators, there was no central Trust log of what clinical trials documentation was in the archive at the time of the flood, and it was unclear what clinical trials data had been damaged, despite it being almost a year since the flood. Commercial sponsors had not been notified because the Trust was not aware of what data/documentation had been affected to date. The inspectors were told that some archived material had been destroyed following the flood, but it was not possible during the inspection to confirm whether this destruction related to clinical trial data or not. It was not clear at the time of the inspection what the impact of this issue was, because the Trust were unaware of exactly which clinical trials had been archived at the facility, and therefore which trials (sponsored and hosted) had been affected by flood damage.

Critical Finding 3

One critical finding was for a Clinical Trials Unit (CTU) that was delegated the role of performing pharmacovigilance activities (including the co-ordination of SAE reporting) on behalf of their two main Sponsors. During their routine QC checks of the data, the CTU found that there were discrepancies in expectedness assessments between the investigator (site) and Chief Investigator (clinical reviewer/sponsor-delegated review conducted by a physician on behalf of the CTU) across all CTU trials [CTU processes required both investigators and clinical reviewer to provide causality and expectedness assessments for SAEs]. A query was sent to the GCP Serious Breaches mailbox requesting advice on whether the issue of discrepancies in expectedness assessments was considered to be a serious breach and should be reported as such. MHRA stated that this issue would be reviewed at the upcoming inspection. At the inspection closing meeting it was discussed with the organisation that the inspectors regarded the issue of inconsistency in the duplicate assessments of expectedness to be a potential critical finding due to the potential for there to have been significant under-reporting of SUSARs across all trials conducted at CTU. However, in order to make an informed decision whether this issue met the definition of a critical finding, the inspectors asked CTU to expedite the ongoing review of impacted cases and provide the outcome to the MHRA. The outcome of this review provided was that 26 cases required upgrading to SUSARs across 5 trials, (and therefore had not been appropriately expedited) and 25 cases required downgrading from SUSARs across 4 trials (and therefore had been inappropriately expedited). Therefore the critical finding was confirmed.

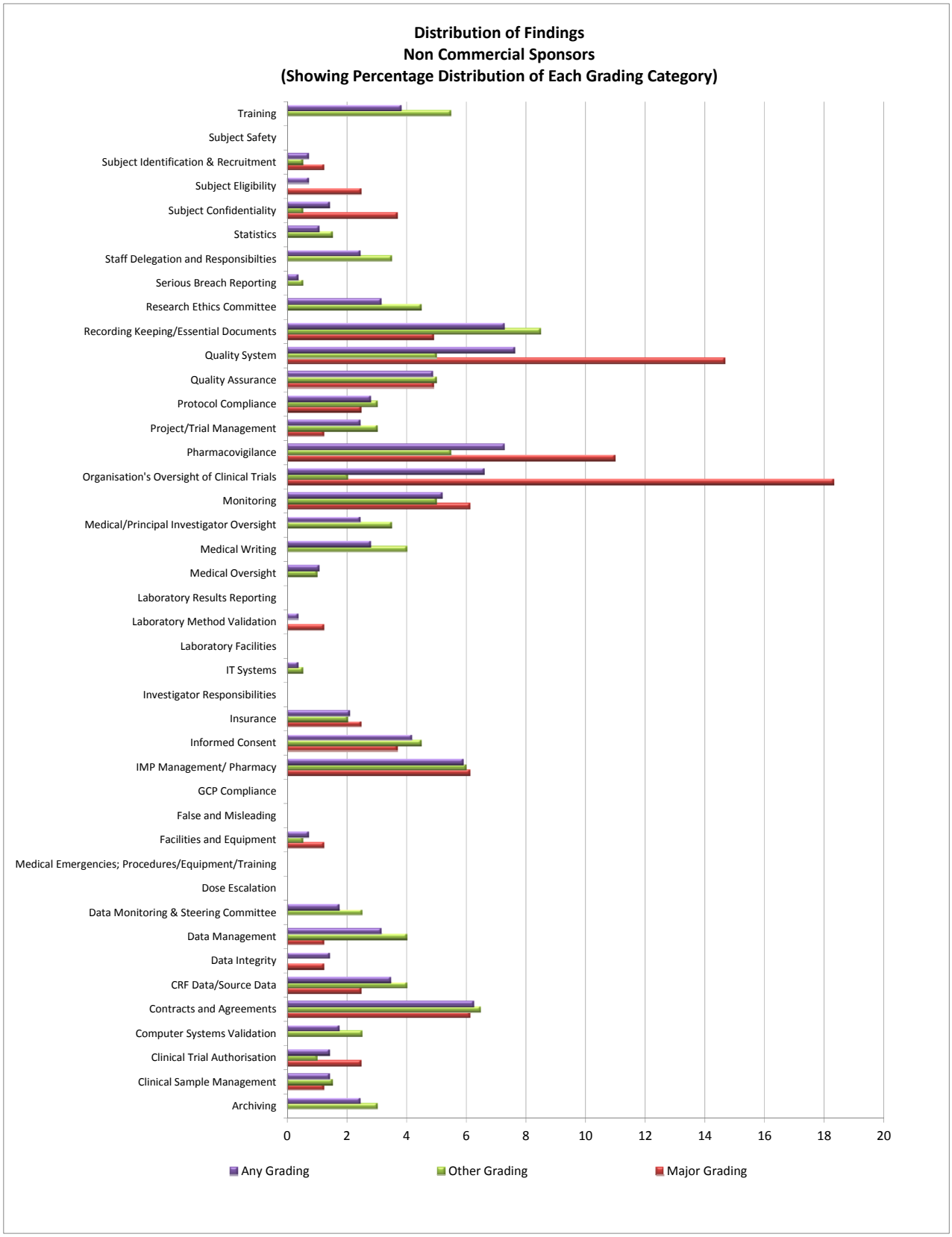
Critical Findings 4, 5 and 6

The MHRA selected a trial for review at a University systems inspection that was co-sponsored by the University and a NHS Foundation Trust. A pre-inspection informal review was conducted by the trial team, a university monitor and by the Trust Quality Assurance manager. This identified that the correct randomisation procedure had not been followed resulting in the majority of patients included in the trial not being correctly randomised to their assigned treatment. This was submitted to the MHRA as a

serious breach. All trials overseen by this Chief Investigator (CI) were temporarily halted and the CI was suspended from conducting any clinical trial activities until further notice. At the inspection, there was a review of the randomisation list against the treatments to which trial subjects had been randomised to (based on the date of the prescription) that showed that this had only been followed for the first 12/43 patients. After these twelve subjects, due to pressures on recruitment, patients had been positively allocated to one arm of the trial if they had made this a condition of their participation (i.e. patients were effectively allowed to choose which treatment arm they wanted, rather than be allocated treatment randomly) in the trial, and then the PI attempted to fill in the spaces with other patients who had not made this a condition of their participation. This was graded and given as a Critical finding for Data Integrity.

Following the outcome of this inspection and additional serious breach notifications provided by the co-sponsors relating to their investigations to date of the study team, it was decided to conduct a second triggered joint inspection of the University and the associated NHS Trust who were co-sponsors, to focus on two more of the CI's trials. Two critical findings associated with Medical / Principal Investigator Oversight and Data Integrity were raised. The first concerned poor oversight by the CI to ensure a robust protocol and procedures for randomisation and IMP management were in place. There was also no documentation to demonstrate the CI's involvement in the oversight and critical decision making associated with either trial. An example where oversight was lacking was that in one trial there had been a lack of timely medical input into patient randomisation and the eligibility decision (which had been made by the trial coordinator who was not a health care professional as defined by the Regulations) which led to only 1 patient being eligible out of the 9 randomised. In the same trial it was not possible to reconstruct which patients had been dosed with which IMP. The second critical finding concerned the issue that across both trials, the data collected and documented was of very poor quality with missing data throughout, including, a large amount of critical data which had not been collected for a variety of reasons (diaries not brought back, equipment availability and failures, blood samples not being taken (especially at baseline). In addition it was identified that members of the trial team, e.g. trial coordinator, for one of the trials were un-blind to the treatment allocation due to the presence of the randomisation schedule in the trial master file, despite the trial being a blinded study. Also, for the other trial the randomisation list had not been followed because subjects were randomised to one arm first, as the IMP had a shorter shelf-life which ultimately defeated the purpose of the randomised double blind design. The CI had been involved in five trials where he had been the CI which have all been halted by the co-sponsors following these issues. He had also been involved in seven hosted trials, but recruitment did not exceed more than 2% of the total population in any of these trials.

The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Non Commercial Sponsors
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
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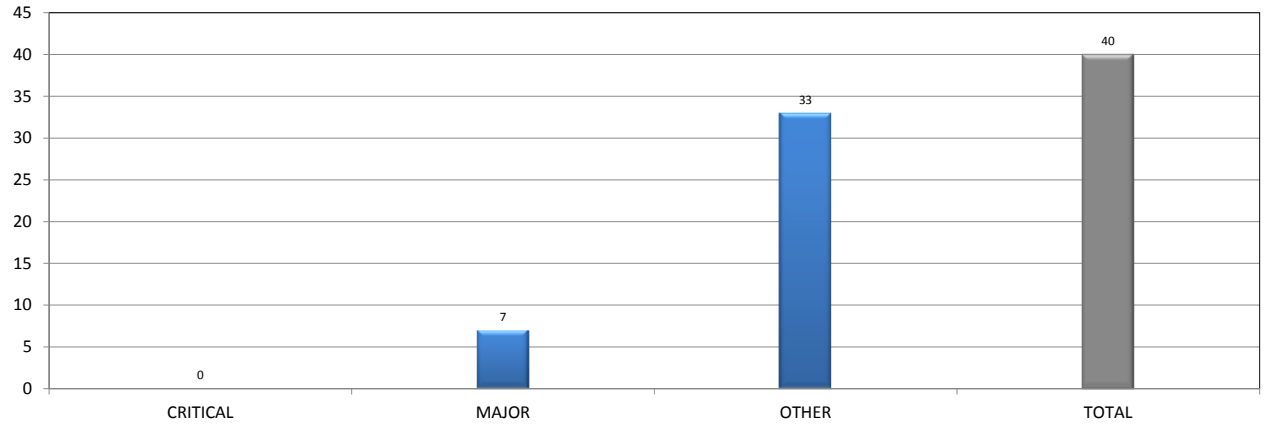
Any Grading
Other Grading
Major Grading

3.4 Commercial Phase 1 Units/Clinical Research Units (Routine Systems and Triggered)

A total of 7 inspections were done of Commercial Phase 1 Units/Clinical Research Units. All but 2 were also routine inspections for the MHRA voluntary phase 1 accreditation scheme. One of the inspections was a "triggered" inspection due to a variation to the accreditation scheme and one further inspection was triggered for non-compliance issues. Note that findings relate to GCP and not those related to the accreditation scheme.

Of the 7 reported inspections, none had a critical finding and 2 (28.6%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below.

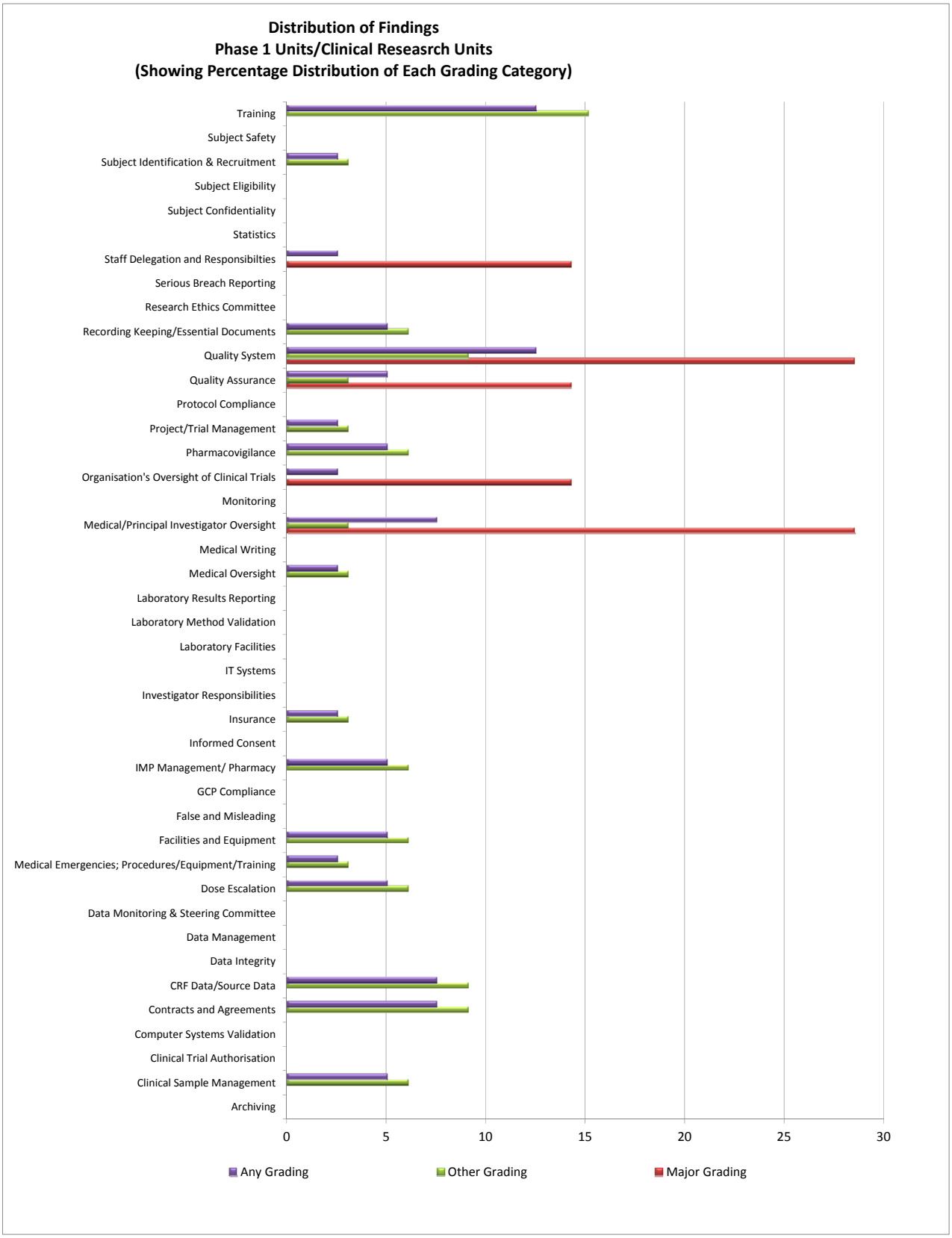
Number of Findings
Phase 1 Units/Clinical Research Units



Number of Findings Per Inspection (Phase 1 Units/Clinical Research Units)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	7
Major	1.0	0.0	0.0	4	7
Other	4.7	6.0	0.0	9	7

The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Phase 1 Units/Clinical Reseasrch Units
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
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Medical/Principal Investigator Oversight
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Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
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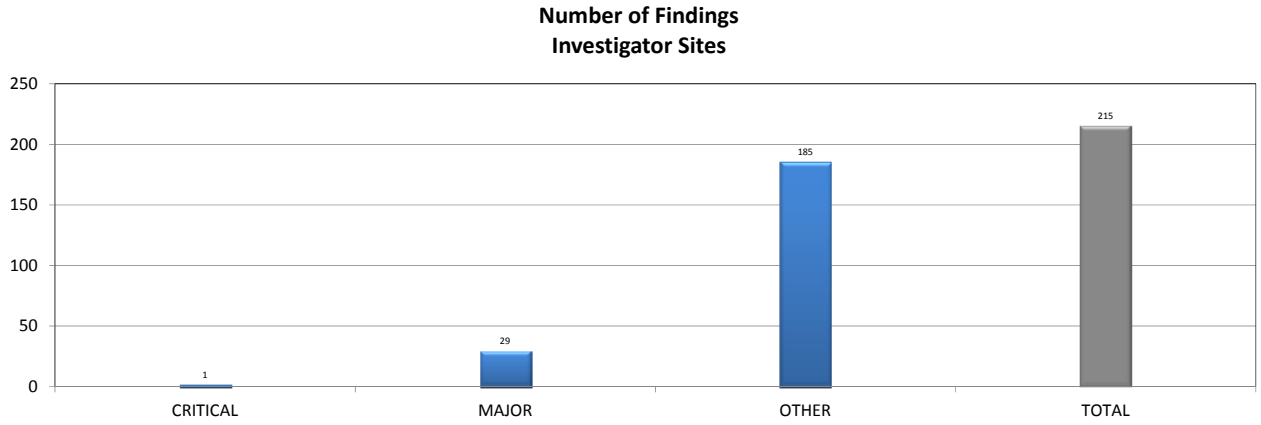
25
30
Any Grading
Other Grading
Major Grading

3.5 Investigator Sites (as part of Commercial/Non-commercial/CRO Routine Systems & Study Specific and Triggered)

A total of 34 investigator sites in the UK were inspected, all except 1 were as an associated site with a sponsor/CRO inspection, the single inspection being triggered as a result of non-compliance.

Of the 34 inspections, 1 (2.9%) had a critical finding, which was from the triggered inspection and 18 (52.9%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below. It should be noted that as associated sites, the emphasis of the inspection was on how the investigator site had been overseen by the sponsor/contracted CRO.



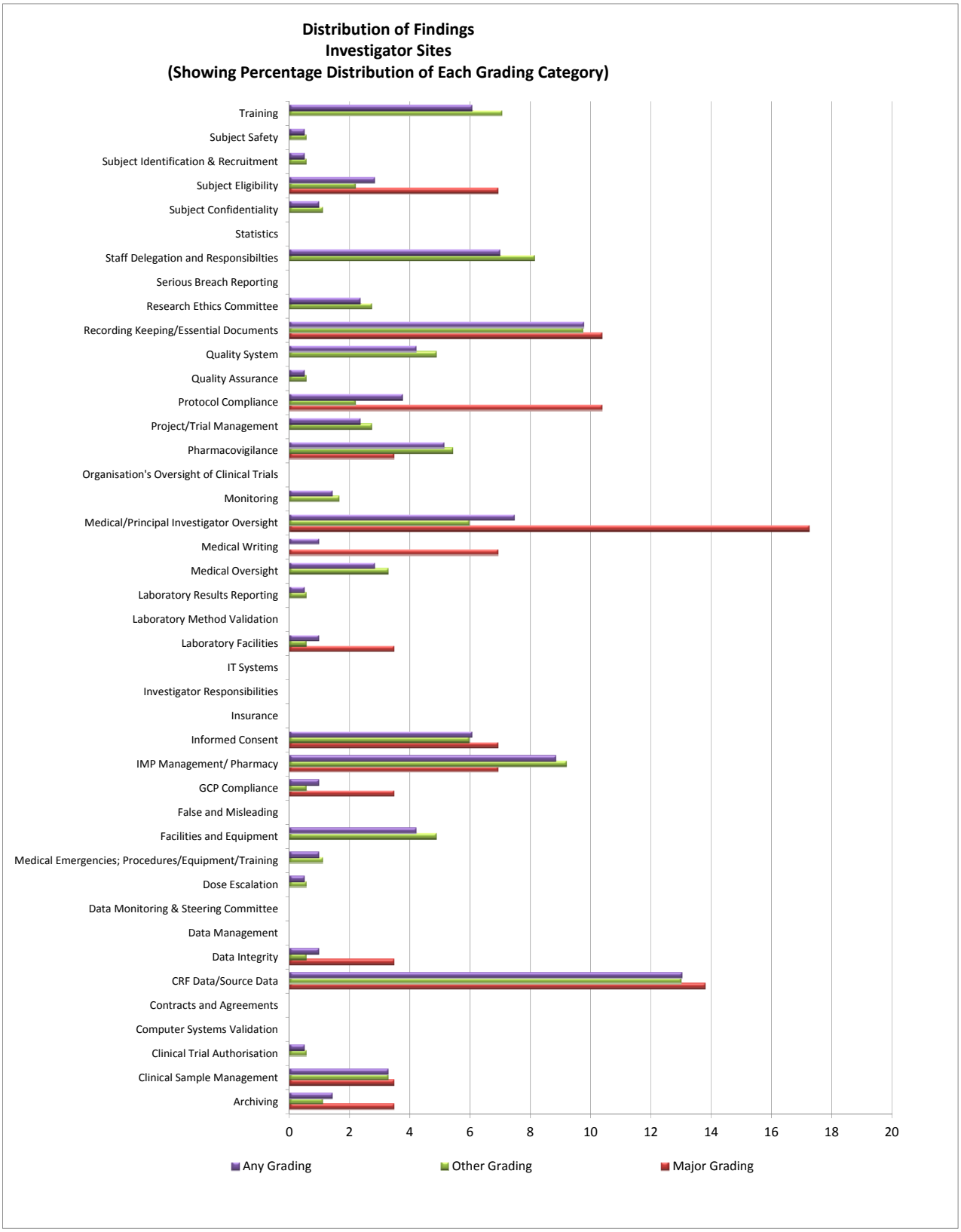
Number of Findings Per Inspection (Investigator Sites)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	1	34
Major	0.9	0.5	0.0	6	34
Other	5.4	6.0	5.0	8	34

Critical Finding

A patient was given IMP from blinded study supplies in the Emergency Room in response to a request for a medicine, instead of from the stock of the medicine from the standard clinical supply available in the room. The patient subsequently died. The study drug was un-blinded and found to be placebo. This was a critical finding as it was a breach of the protocol and GCP because the patient was not eligible for the trial, due to age and indication, there was no consideration given to consent and the staff administering the IMP were not trained to do so, and were not delegated this task by the PI. It is understood that the patient's condition was very serious, and the inspectors were told that it is unlikely that receiving the medicine rather than a placebo would have made a difference to the patient's outcome.

The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Investigator Sites
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
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Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
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Informed Consent
IMP Management/ Pharmacy
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False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
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Data Integrity
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Clinical Trial Authorisation
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Archiving
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Any Grading
Other Grading
Major Grading